Cancer Chemother Pharmacol (1982) 9: 17–21

Cancer Chemotherapy and Pharmacology

Therapy of Liver Tumors Metastatic from Colorectal Cancer with Whole-Liver Radiation Combined with 5-FU, Adriamycin, and Methotrexate

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Summary. *Twenty-seven patients with liver metastasis from colorectal cancer were treated with intrahepatic arterial chemotherapy and external radiotherapy consisting of 5-fluorouracil (5-FU) (10 mg/kg/day for 8 days), adriamycin (5 mg/m²/day for 7 days) and methotrexate (MTX) (240 mg/m²/X1), combined with 2,100 rads of whole liver irradiation. Twenty of these patients (74%) had previously received systemic chemotherapy. Of the 21 patients who could be fully evaluated, seven (33%) had an objective partial response and another 10 (48%) had stable disease following treatment. The median duration of survival for all patients after initiation of treatment was 6.5 months. Those patients responding to therapy survived longer (12.7 months) than those who had stable disease (5.5 months) or disease progression (2.5 months). The response rate was not affected by previous chemotherapy. Additionally, of the 14 patients with symptoms related to the disease, nine (64%) experienced substantial relief of these symptoms. Toxicity with the therapy used in this study was generally moderate. The median nadir WBC was 3,500 cells/mm³; the median nadir platelet count, 121,000 cells/mm³. There was, however, one treatment-associated fatality from sepsis in a patient whose WBC was 900 cells/mm³.*

Introduction

Hepatic metastasis from colorectal malignancy is a frequent cause of cancer-related morbidity and mortality. Colorectal tumors metastatic to the liver are rarely curable surgically, and because systemic chemotherapy is seldom effective, regional therapies have often been attempted for their control. We have investigated the use of external radiotherapy combined with intra-arterial chemotherapy for the treatment of these resistant tumors. Initially, we studied the combination of 5-FU and adriamycin given via the common hepatic artery, administered concurrently with 1,500–2,100 rads of whole-liver irradiation. As previously reported, this treatment was efficacious, safe, and required only a single brief hospitalization [11]. In our current study, we hoped to improve the response by adding a moderate dose of MTX (Fig. 1). This drug was chosen because it has been shown to have synergistic activity with 5-FU in vitro [7]. We also included leucovorin rescue in the treatment protocol to minimize the systemic toxicity of MTX. This report presents the results of a phase I–II Northern California Oncology Group study in which external whole-liver irradiation was combined with intra-arterial 5-FU, adriamycin, MTX, and leucovorin rescue for the therapy of liver tumors metastatic from colorectal cancer.

Radiation therapy

2,100 Rads to whole liver in 300 rad fractions daily

Chemotherapy via common hepatic artery

5-Fluorouracil – 10 mg/kg/day continuous infusion × 8 days

Methotrexate – 240 mg/m² day 1 only

Adriamycin – 5 mg/m²/day × 7 2 h prior to radiation therapy

Fig. 1. Combination therapy of liver metastases

Materials and Methods

Patient Selection. The criteria for patient selection were (a) biopsy-confirmed colorectal cancer with liver metastasis documented by biopsy or scan; (b) disease measurable by physical examination, radionuclide or computerized tomographic (CT) scan; (c) age ≥ 16 years and ≤ 75 years;, (d) Karnofsky performance status (KPS) of ≥ 50%; (e) normal renal function (BUN of ≤ 30 mg%, serum creatinine levels ≤ 1.8 mg%); (f) WBC ≥ 4,000/mm³, platelet count ≥ 100,000 cell/mm³; (g) expected survival of ≥ 6 weeks; (h) no previous hepatic arterial chemotherapy or radiation to the involved field; (i) no pre-existing cardiac disease that would preclude the use of adriamycin; (j) no ascites or effusion that would preclude the safe use of MTX; and (k) signed, informed consent.

Previous systemic chemotherapy was not deemed a contraindication for entry into this study, irrespective of response.

Criteria of Response. Objective response was determined by liver scan (either radionuclide or CT) and estimation of the liver size by palpation. Liver function tests and serum CEA levels, although obtained in most patients, were not used as criteria of response. Partial response was defined as either a decrease of at least 50% in the product of the largest perpendicular dimensions of tumor on scan, or a decrease of at least 30% in the sum of three measurements of liver size. These measurements were determined by palpation of the liver below the xiphoid process and below each costal margin in the midclavicular lines. To be considered a response these

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0344-5704/82/0009/0017/$ 01.00

improvements were required to have been sustained for at least one month. Progressive disease was defined as the appearance of new lesions, or an increase of 15% or more in tumor size measured by scan or palpation as described above. Patients not meeting the criteria for response or progression were judged to have stable disease. Symptoms reported by patients before and after therapy were also recorded. Duration of survival was measured from initiation of therapy.

Chemotherapy. Intrahepatic arterial catheters were placed via the femoral or brachial artery under fluoroscopic control. After complete hepatic arteriograms were obtained, the catheters were sutured in position, with the catheter tip placed in the common hepatic artery or as close to that position as possible. Catheter placement was rechecked at least once. Line patency was maintained by the inclusion of 4,000 μ heparin/liter.

Generally, patients received radiotherapy on 6 days per week. Two hours before the first treatment and before each subsequent radiation treatment they received adriamycin through an intrahepatic arterial catheter as a slow bolus injection. Adriamycin was given only on days when radiation was administered. The standard dose of adriamycin was 5 mg/m^2/day for 7 days. Patients who had had previous chemotherapy received a standard dose of 3 mg/m^2/day. In all cases, when serum bilirubin levels were elevated the adriamycin dose was decreased (50% for bilirubin levels of $\geq$ 1.5 mg%, but $\leq$ 3.0 mg%; 75% for bilirubin levels of $>$ 3.0 mg%). Adriamycin dosage was also decreased in instances of severe myelosuppression.

Immediately after the first dose of radiation an alkaline diuresis was established with saline, sodium bicarbonate, and if necessary, acetazolamide. MTX was then administered via the intrahepatic arterial catheter as a 90 mg/m^2 bolus, followed by a 150 mg/m^2 infusion. MTX was given only on the first day of therapy, and MTX levels were drawn at 0, 6, 24, and in some cases, 48 h after MTX infusion. The pharmacokinetics of these levels have been reported elsewhere [14].

5-FU was given as a continuous infusion of 10 mg/kg/day through the intrahepatic arterial catheter with an IVAC pump. 5-FU was begun immediately after the MTX infusion was completed. The dose of 5-FU for each 24-h period was mixed in 1,000 cm^3 D_5W, with 4,000 units heparin added. 5-FU infusion was continued for the entire duration of therapy (including days on which no radiotherapy was given) and was interrupted only for the adriamycin injection.

Leucovorin. Leucovorin (25 mg/m^2) was administered PO or IV every 6 h, beginning 24 h after completion of the MTX infusions. Leucovorin was continued for 12 doses.

Radiotherapy. The entire liver was irradiated using AP/PA fields established on a simulator and determined by palpation, angiographic films, and scan (either radionuclide or CT). Both fields were treated each day, using a 4 MeV or ^{60}Co machine at 80 cm SSD at 100–300 rads/min. Treatment was given in 300 rad fractions, central axis dose, to a total dose of 2,100 rads. At least one-third of the total renal volume was protected by blocks, usually placed over the lower part of the left kidney.

Complete blood counts, platelet counts, and chemistry profiles were obtained at initiation of therapy and daily during treatment for evidence of systemic toxicity. After completion of therapy, the above checks were carried out at 1–2 week intervals. Four weeks after completion of the protocol treatment the response of patients was evaluated by the parameters previously described. After this evaluation subjects either did or did not receive additional systemic therapy, at their physicians' discretion. For the purpose of this study, parameters of response continued to be monitored, usually at 1-month intervals, until disease progression occurred.

Results

Patient Characteristics

Twenty-seven patients with liver metastases from colorectal cancer were entered into this study between July 1978 and May 1979 (Fig. 2). Patients with primary hepatocellular cancer and metastatic disease from non-colon primary sites were similarly treated but not included in this analysis. Two of the 27 patients entered into this study were considered to have been ineligible; one because of age and pre-existing cardiac disease, one because of ascites. Details of characteristics of the 25 eligible patients are presented in Table 1. In addition to the two patients ineligible for study (and thus excluded from all analysis), the responses of four of the original 27 patients were judged to be inevaluable, two because patients were lost to follow-up and two because of major protocol violations. These four inevaluable patients were, however, included in analysis of toxicity. Of the 25 patients who were eligible for this therapy, 19 (76%) had had previous chemotherapy. There were 17 male and eight female patients; all were between the ages of 32 and 72 years (median age, 61 years). One patient was black, one was Filipino, and the remainder were white. The median time from original diagnosis of cancer to study entry was 4 months. The median KPS was 80%. At the initiation of therapy, of the 21 patients who were evaluated 14 (67%) had symptoms related to the disease (primarily right upper quadrant abdominal pain).

As summarized in Table 1, of the 21 evaluable patients seven (33%) had partial responses; 10 patients (48%) had stable disease after therapy; and four patients (19%) experienced early disease progression. Follow-up continued in all patients to time of death. Median duration of survival after initiation of therapy for all 21 patients evaluable for response was 6.5 months (range: 0.7–29.1 months). Median survival after therapy in responding patients (12.7 months) was longer than in patients temporarily stable (5.5 months) or in patients with disease progression (2.5 months). The difference in survival between responders and non-responders was not significant by Gehans' modified Wilcoxon procedure ($P = 0.14$, two-tailed test) [12]. The median duration of survival from the original diagnosis of cancer was 24.8 months for all evaluated patients and was not significantly different for responders vs non-responders. Also, the median duration from diagnosis of hepatic metastases to therapy was 3.75 months in responders, as against 8.5 months in those with early disease progression. These facts suggest that the longer survival from treatment in responders may have been the result of therapy applied earlier in the illness, rather than a true benefit of the intervention. The response rate did not appear to be greatly affected by previous chemotherapy, since only two of the six patients not previously treated responded in this study. After therapy, relief of symptoms was reported in nine of 14 patients (64%) who initially had symptoms. In general, this symptomatic relief was dramatic and prolonged.

Table 1. Patient characteristics

Patient	Age/sex	Previous chemotherapy	Response to therapy of study[a]	Survival after diagnosis (mo.)[a]	Survival after therapy (mo.)[a]
RO	56/M	None	S	23.1	21.5
RH	32/M	5-FU, MeCCNU, VCR	PR	29.3	15.1
LB	70/F	5-FU	PR	1+[d]	1+[d]
SH	52/M	5-FU, MeCCNU	S	25.1	2.5
AS	71/F	5-FU, MTX	NE[b]	9.8	2.4
RE	53/M	5-FU, MeCCNU	S	41.5	10.9
JV	61/M	5-FU, MeCCNU	PR	49.7	12.7
EA	59/M	5-FU, MTX	P	13.2	1.3
JB	59/M	5-FU	P	17.9	13.7
BF	56/F	None	PR	18.4	13.2
GJ	63/F	None	S	66.5	6.5
EO	63/M	5-FU, MeCCNU	S	101.4	29.1
CW	61/M	5-FU	S	12.1	1.6
MG	67/M	5-FU	P	11.2	1.4
GC	53/M	5-FU, Chlorambucil	S	28.3	4.6
WC	72/M	None	PR	19.1	17.9
JA	53/M	5-FU	S	24.8	2.5
AG	62/M	MeCCNU	PR	26.3	12.1
EB	62/F	5-FU, MeCCNU, MMC	NE[c]		
LS	62/M	5-FU, MeCCNU	PR	26.6	5.0
RC	53/M	5-FU, MeCCNU	P	54.7	3.5
KB	59/F	None	S	28.4	0.7
SW	63/M	5-FU	NE[c]		
ER	50/F	None	S	24.0	23.0
GS	64/F	5-FU	NR[b]	10.9	4.2

[a] S, stable disease; PR, partial response; NE, not evaluable; P, progression
[b] Major protocol violation
[c] Unavailable for assessment before response evaluated
[d] Unavailable for assessment after response evaluated

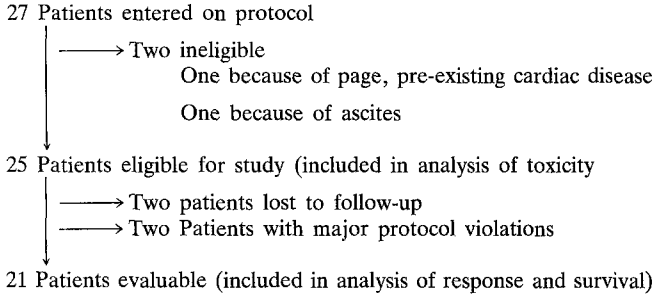

Fig. 2. Schema of patients studied

Table 2. Toxicity of combined therapy[a]

	Median nadir	Range
Hematologic:		
WBC	$3.5 \times 10^3/mm^3$[b]	900–15,900
Platelet	$112{,}000/mm^3$	10–326
Hemoglobin	9.0 g/dl	6.4–12
	No. experiencing	**No. in whom severe**
Other:		
Nausea/vomiting	19/25	2
Mucositis	7	3
Hepatic	2	0
Alopecia	0	

[a] Toxicity summarized for all 25 patients eligible for study even if not evaluable for response
[b] One patient who had a WBC of 900 cells/mm^3 died of sepsis

Hematologic Toxicity

The effect of therapy on the peripheral blood was minimal (see Table 2). Median nadir WBC was $3.5 \times 10^3/mm^3$; median nadir platelet count, $112{,}000/mm^3$; and median nadir hemoglobin level, 9 g/dl. Mild therapy-related hemorrhage was recorded in four patients, but in all cases this consisted of clinically insignificant bleeding at the arterial catheter site. Despite the use of intra-arterial catheters in this therapy, no thrombotic or embolic events were observed, although it is impossible to exclude such events if the size of an embolus is sufficiently small. Severe treatment-associated infection was noted in one patient in whom sepsis was the presumed cause of death (WBC: 900 cells/mm^3). One patient was febrile at the beginning of therapy; presumably fever was secondary to the presence of tumor. Of 24 patients afebrile at entry, 15 experienced fever during treatment. Treatment-associated fever was graded as mild to moderate in 12 patients, and severe in three. These patients all became afebrile soon after completion of treatment.

Non-Hematologic Toxicity (see Table 2)

Nausea and vomiting occurred in 19 of 25 patients. In 17 of these, symptoms were graded as mild to moderate in severity. Anorexia and fatigue were also common during therapy, but

were mild and temporary. Two patients had moderately severe hepatic toxicity associated with this therapy. Also, transient elevations in tests of liver function were common, although most returned to, or fell below, pretreatment levels. In a review of tissue obtained at autopsy, we found no evidence of radiation hepatitis. Mucositis was seen in seven patients and was severe in three. Alopecia was not observed. Catheter-associated complications were limited to occasional problems with maintenance of tip position in the common hepatic artery. This was frequently seen early in the study, when most catheters were placed via the brachial artery. Subsequently, the femoral arterial approach was used. It should be noted that two patients who received this therapy for tumors of other primary sites died of hepatic failure temporally related to therapy.

Discussion

The liver is a common site of metastasis from colorectal cancer, and the resultant hepatic tumors are responsible for mortality and preterminal morbidity in thousands of patients yearly. The natural history of hepatic metastasis is well documented and the diagnosis carries a grave prognosis [3, 15, 18, 21]. Untreated patients have an expected survival of approximately 4–6 months, although it is frequently difficult to compare clinical series because of variations in patient population and study design.

The inadequacy of therapy for liver metastasis reflects our present difficulty in treating the primary tumor. Systemic therapy with 5-FU, the most active agent in colon cancer, results in an approximate 20% objective response rate, with little impact on survival [18, 26]. Other chemotherapeutic agents are even less active. Furthermore, no benefit appears to accrue from the use of combinations of these drugs with 5-FU [25].

Because the liver is often the only site of relapse in colon cancer, chemotherapy is frequently administered directly to the tumor via the common hepatic artery. Objective response rates may be improved by this technique, but there continues to be disagreement on this issue. It has been variously reported that 35%–80% of patients benefit from the use of short- or long-term intra-arterial infusions of 5-FU or FUDR [1, 2, 4, 8, 20, 22]. It is notoriously difficult, however, to reproducibly measure a change in the size of hepatic tumors, and this disadvantage, combined with the various definitions of response in different reports, makes it difficult to compare results. The duration of survival after treatment may be a more meaningful measurement of the effect of therapy. Patients not responding to intra-arterial infusions are reported to have a median survival of from 1–5 months, as against a median survival in responding patients of 8–12 months [1, 4, 10].

Objective responses and survival rates comparable to those achieved with intra-arterial chemotherapy have been reported with the use of external whole-liver radiation [23, 24, 27, 28]. Additionally, radiotherapy has been effective in palliating the pain of liver tumors metastatic from colon cancer, an important problem often not addressed in reports of chemotherapy.

In an attempt to develop a more effective therapy for patients with metastasis from colorectal cancer, we have used combinations of intrahepatic arterial chemotherapy and external liver irradiation. We previously reported our initial results using intra-arterial 5-FU and adriamycin combined with 1,500–2,100 rads delivered over 6–8 days [11]. We used this combination of drugs for several reasons: 5-FU was chosen because of its proven activity in these tumors when used intra-arterially, and because it has been reported to potentiate the effect of radiotherapy [17, 19]. Adriamycin can also enhance radiation effect [5, 6, 8], and we hoped its rapid hepatic uptake would limit systemic toxicity when given via the hepatic artery [9, 13, 16]. When we used this combination for patients with hepatic metastasis we achieved a 55% objective response rate, symptomatic relief in 80% of patients, a minimum of hematotoxicity, and no radiation hepatitis. We based our current study on this previous experience, adding intra-arterial MTX in an attempt to improve the response rate. We administered this therapy to 27 patients with liver metastasis from colon cancer and achieved a response which was comparable to that seen in our initial protocol. Seven of the 21 patients we could evaluate (33%) had an objective partial response, and another 14 (48%) had stable disease. Those patients whose disease responded to therapy survived longer (12.7 months) than those whose disease was stable (5.5 months) or had progressed (2.5 months). No therapy was specified for patients after completion of this trial, and subsequent treatment was left to the discretion of the referring physician. We feel that this uncontrolled variable is unlikely to have had a major impact on duration of survival. As in our previous phase I–II trial, in this study we were again gratified to observe symptomatic relief, which occurred in nine of 14 patients. Pain was the most common presenting symptom, and relief of this and other symptoms was rapid and prolonged.

The toxicity of this therapy was somewhat greater than anticipated. Although hematotoxicity was generally not severe, there were exceptions. One patient died of sepsis, and had a WBC of 900 cells/mm^3. Moderate hepatic deterioration occurred in two patients. Additionally, two patients who had liver metastasis from other primary sites (and were therefore not included in this analysis) experienced fatal hepatic failure after receiving similar therapy. The relationship of hepatic toxicity in our patients to therapy is unclear, since we have not been able to document radiation hepatitis in patients treated with this combination. In general, toxicity did not necessitate interruption of therapy or dose reduction.

We believe that a combination of intrahepatic arterial chemotherapy and external liver irradiation can be used in the treatment of hepatic tumors, but we cannot determine from this study how this or similar combinations of radiotherapy and chemotherapy should be best utilized. In this series the addition of MTX to the combination of 5-FU and adriamycin, which we had used previously, appeared to increase the toxicity of therapy without improving the response rate; thus the use of MTX has been discontinued.

We are currently conducting a prospective randomized trial comparing radiation therapy alone with combinations of radiation therapy and chemotherapy given either by intra-arterial or intravenous routes.

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Received November 24, 1981/Accepted April 5, 1982